IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Robert M. Jones et al.	Art Unit	: 1624
Serial No.	: 10/541,657	Examiner	: Jeffrey H. Murray
Filed	: March 3, 2006	Conf. No.	: 4098
Title	: 1,2,3-TRISUBSTITUTED ARYL AND HETEROARYL DERIVATIVES AS MODULATORS OF METABOLISM AND THE PROPHYLAXIS AND TREATMENT OF DISORDERS RELATED THERETO SUCH AS DIABETES AND HYPERGLYCEMIA		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION UNDER 37 C.F.R. § 1.181

Applicant hereby petitions the Technology Center Director under 37 C.F.R. § 1.181 to review the finality of the Office Action of December 17, 2009 and respectfully requests that the finality of the Office Action be withdrawn. Applicants also ask that the propriety of the Office Actions dated March 9, 2009 and December 17, 2009 be considered, and whether either or both of these Office Actions should be vacated in light of the facts described herein.

I. Statement of Facts

The above-captioned application was filed under 35 U.S.C. § 371 on March 3, 2006 as the U.S. National Phase of International Application PCT/US2004/001267.

A first Office Action on the merits was issued on March 9, 2009. The following rejections were made:

1. Claims 1-3, 9, 11-61, 70, 72-76 and 78 were rejected under the enablement requirement of 35 U.S.C. § 112, first paragraph. The rejection stated, among other things, that the "Applicant has demonstrated within the application how to make triazolopyrimidines and pyrazolopyrimidines" even though the present application does not discuss such compounds. Office Action dated March 9, 2009, pp. 6-10.
2. Claims 1-3, 9, 11-61, 70, 72-76 and 78 were rejected under 35 U.S.C. § 112, second paragraph as being allegedly indefinite due to the use of allegedly unclear terms. The allegedly unclear terms were "heteroaryl", "heterocycloalkyl" (and "terms containing contain these terms, such as 'heterobicycloalkyl,' 'heterobicycloalkylalkyl' or

'heterocycloalkylalkyl.'"), "carboxy" and "agonist compound." Office Action dated March 9, 2009, pp. 10-12.

3. Claims 1-3, 9, 12, 14-17, 32, 39, 41, 42 and 70 under 35 U.S.C. § 102(b) over a reference by Cocco. Office Action dated March 9, 2009, pp. 13-14.

Applicants filed a response on June 9, 2009, traversing both the enablement and indefiniteness rejections. Applicants traversed the enablement rejection pointing out, *inter alia*, that the rejection improperly disregarded the presumption of enablement; that the reasons given for the rejection did not appear to relate to the disclosure of the present application (since it stated that the guidance provided in the application demonstrated how to make triazolopyrimidines and pyrazolopyrimidines, which are not specifically discussed in the application). Applicants provided a detailed discussion of each of the *Wands* factors as applied to the claims. *See* Response to Office Action Dated March 9, 2009, filed June 9, 2009 at pp. 44-60. Applicants also traversed the indefiniteness rejection, pointing out that the term "heteroaryl" was defined in the specification (on p. 16) and that the term "heterocycloalkyl" did not appear in the application. *See* Response to Office Action Dated March 9, 2009, filed June 9, 2009 at pp. 63-64.

On December 17, 2009, a further Office Action was issued that was made final. The following rejections were made:

1. Claims 1-3, 12-14, 16-61, 73, 74 and 78 were rejected under the enablement requirement of 35 U.S.C. § 112, first paragraph. The Office Action characterized the reference in the prior Office Action to "triazolopyrimidines and pyrazolopyrimidines" as a "typographical error". Office Action dated December 17, 2009 at p. 2 lines 13-15.
2. Claims 1-3, 9, 11-61, 70, 72-76 and 78 were rejected under 35 U.S.C. § 112, second paragraph as being allegedly indefinite due to the inclusion of allegedly unclear terms. The Office Action continued to allege that the term "heteroaryl" was unclear. However, the Examiner presented a **new reason** that the claims were unclear, namely that the **new** term "heterocyclic" was allegedly not clear. The Examiner indicated that Applicants were "correct in noting examiner made a typographical error in using the term "heterocycloalkyl" and not "heterocyclic." Office Action dated December 17, 2009 at p. 4 lines 12-13.

3. Claims 1-3, 12, 16 and 78 were rejected under 35 U.S.C. § 102(e) as being anticipated by Griffith. Office Action dated December 17, 2009 at p. 5.

The Office Action stated that it was made final because Applicants' amendment "necessitated the new ground(s) of rejection presented in this Office action." Office Action dated December 17, 2009 at p. 6 lines 1-2.

Applicants have learned of an Office Action in another Application, passages from which were apparently copied word-for-word into the Office Action mailed on March 9, 2009 in the present application, even though portions of the copied text were clearly inapplicable to the present application. The Office Action issued in Application 12/001,043, which belongs to a different assignee, claims different subject matter, and is entirely unrelated to the present application, except that it is assigned to the same Examiner for examination. The Office Action was dated March 6, 2009, just three days prior to the issuance of the Office Action dated March 9, 2009 in the present application, and both Office Actions were signed by the same Examiners. Applicants learned of this Office Action on February 14, 2010.

A side-by-side comparison of the certain paragraphs from the Office Action dated March 6, 2009 from Application 12/001,043 with paragraphs of the Office Action dated March 9, 2009 in the present application appears in Appendix A to this Petition and the complete Office Action from Application 12/001,043 appears in Appendix B to this Petition.

Despite the fact that the present application and Application 12/001,043 are unrelated, the two Office Actions bear striking similarities. The paragraph beginning on page 7 line 9 of the Office Action dated March 9, 2009 in the present application was a word-for-word reproduction of the paragraph beginning on page 6 line 1 of the Office Action dated March 6, 2009 in Application 12/001,043, and recited that the application "demonstrated ... how to make triazolopyrimidines and pyrazolopyrimidines." The present application does not include, in fact, any specific discussion of how to make triazolopyrimidines or pyrazolopyrimidines. In similar vein, the two paragraphs beginning on page 11 line 4 of the Office Action dated March 9, 2009 in the present application was almost word-for-word identical to the paragraph beginning on page 12 line 12 of the Office Action dated March 6, 2009 in Application 12/001,043, and recited that "[t]he scope of'heteroaryl' and 'heterocycloalkyl' requires clarification." The reproduced passage went on to allege that these terms had been "defined with non-limiting examples." In

fact, the term "heterocycloalkyl" did not even occur in the claims or specification of the present application, and, furthermore, the term "heteroaryl" was not defined by examples (the term was defined as "an aromatic ring system that may be a single ring, two fused rings or three fused rings containing carbons and at least one ring heteroatom selected from O, S and N." See p. 16 of the Specification.

Indeed, comparing the enablement rejections beginning on p. 6 of the present application with the enablement rejection beginning on p. 7 of the Office Action in Application 12/001,043, it is clear that the rejection in the present application was prepared with only minor alteration from the form prepared for Application 12/001,043. Similarly the indefiniteness rejection regarding "heteroaryl" and "heterocycloalkyl" in the present application was reproduced almost verbatim, despite the significant differences between the claims and disclosures of the two applications, and the fact that the present application does not use the term "heterocycloalkyl".

II. Points to be Reviewed and Action Requested

The Director is respectfully requested to review whether the Office Action mailed December 17, 2009 was properly made final when it contained a new ground of rejection neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c). If the Director agrees with the applicants that the finality was premature, Applicants ask that the finality of the Office Action of December 17, 2009 be withdrawn.

The Director is also respectfully requested to review whether the record indicates that the present application has been examined in accord with Office procedures and policy when (1) the Office Action dated March 9, 2009 contained paragraphs that were clearly inapplicable to the present application, and which the evidence suggests were merely pasted verbatim from an earlier Office Action in a different and unrelated application; and (2) the Office Action dated December 17, 2009 failed to address and answer the substance of Applicants' response (including the suggestion that portions of the earlier Office Action appeared to relate to a different application from the present application). If the Director agrees that the record does not indicate the present application been examined in accord with Office procedures and policy, the

Director is asked to consider whether the Office Action dated March 9, 2009 or the Office Action dated December 17, 2009, or both, should be vacated.

III. Arguments

A. Finality of the Office Action

Under the procedures described in the MPEP, although second or subsequent Office Actions may be made final, it is not proper for an Office Action to be made which "introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c)." *See* MPEP 706.07(a). The MPEP, in fact, specifically states that "a final rejection is improper where there is another new ground of rejection introduced by the examiner which was not necessitated by amendment to the claims nor based on information submitted in an information disclosure statement during the period set forth in 37 CFR 1.97(c)." *Id.* (Examiner Note to form paragraph 7.40.02).

A "ground of rejection" includes "not merely the statutory requirement for patentability that a claim fails to meet but also the precise reason why the claim fails that requirement." *See Hyatt v. Dudas*, 551 F.3d 1307, 1312 (Fed. Cir. 2008).

Furthermore, the MPEP emphasizes:

> The examiner should never lose sight of the fact that in every case the applicant is entitled to a full and fair hearing, and that a clear issue between applicant and examiner should be developed, if possible, before appeal.

MPEP 706.07.

Applicants respectfully submit that the Office Action mailed on December 17, 2009 was not properly made final because the Office Action included a new ground or rejection that was neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c).

The new ground of rejection was a new reason presented for the rejection of 1-3, 9, 11-61, 70, 72-76 and 78 under 35 U.S.C. § 112, second paragraph as being allegedly indefinite. The Office Action of December 17, 2009 alleged that these claims were indefinite, in part because the claims use the term "heterocyclic" which the Examiner alleged was "defined vaguely with non-limiting examples." Office Action dated December 17, 2009, p. 4 lines 12-15.

This allegation that the claims were indefinite due to use of the term "heterocyclic" was made for the first time in the Office Action dated December 17, 2009. Although the Office Action dated March 9, 2009 had also rejected claims 1-3, 9, 11-61, 70, 72-76 and 78 as being allegedly indefinite, the terms alleged to have been indefinite in the Office Action of March 9, 2009 were "heteroaryl", "heterocycloalkyl" (and "terms containing these terms, such as 'heterobicycloalkyl,' 'heterobicycloalkylalkyl' or 'heterocycloalkylalkyl.'"), "carboxy" and "agonist compound." The alleged indefiniteness of the term "heterocyclic" was presented as a new reason for rejecting the claims in the Office Action of December 17, 2009.

In explaining the new rejection made in the Office Action dated December 17, 2009, the Examiner stated that Applicants were "correct in noting examiner made a typographical error in using the term 'heterocycloalkyl' and not 'heterocyclic." Office Action dated December 17, 2009 at p. 4, lines 13-14. However, this explanation mischaracterized Applicants' response to the allegation Office Action dated March 9, 2009, which had pointed out that "the terms "heterocycloalkyl", "heterobicycloalkyl," "heterobicycloalkylalkyl" or "heterocycloalkylalkyl" are not used in the claims or used or defined in the specification of the present application" and that "[i]t would appear that the Office's remarks regarding these terms [i.e. heterocycloalkyl, etc] are referring to a different application from that which is presently under examination." Response to Office Action Dated March 9, 2009, filed June 9, 2009 at p. 63 line 13-19.

Regardless of the source of the error, however, the Office Action dated December 17, 2009 clearly acknowledged that Applicants were correct in their assessment that the allegedly unclear terms "heterocycloalkyl", "heterobicycloalkyl," "heterobicycloalkylalkyl" and "heterocycloalkylalkyl" did not appear in the claims of the present application, and that this ground of rejection made in the Office Action dated March 9, 2009 had therefore been incorrect.

The Office Action dated December 17, 2009 instead of merely withdrawing the rejection insofar as alleged that "heterocycloalkyl" was indefinite, substituted a new ground of rejection, by alleging that the claims were indefinite because the term "heterocyclic" used in the claims is unclear. Applicants have been provided with no opportunity to respond to this new ground of rejection. If Applicants had been presented with this ground of rejection originally, Applicants could have responded, for example, by pointing to the clear definition on p. 16 of the specification, amending the claims to further clarify them, or submitting a declaration or other

evidence showing that the meaning of term would be apparent and clear to the person skilled in the art. Since the Office Action was made final, Applicants would be denied the opportunity to respond fully as of right, and Applicants have therefore been denied a full and fair hearing and the opportunity to fully develop this issue for appeal.

This is a new ground of rejection because the Examiner is making a new rejection over the term "heterocyclic" which was not part of the rejection in the previous office action. The Examiner contends that he made a mistake by previously reciting "heterocycloalkyl" instead of "heterocyclic", but these terms have are different and Applicants would have no reason to know or even guess that the Examiner meant "heterocyclic" when he wrote "heterocycloalkyl." Thus the Examiner's "correction" in the final office Action was a new ground of rejection.

Applicants therefore respectfully submit that the Office Action dated December 17, 2009 was improperly made final, and that the finality of the Office Action should be withdrawn.

B. Propriety of the Office Actions Dated March 9, 2009 and December 17, 2009

Under the procedures described in the MPEP, "[o]n taking up an application for examination or a patent in a reexamination proceeding, the examiner shall make a thorough study thereof." 37 C.F.R. § 1.104. "[T]o provide a complete application file history and to enhance the clarity of the prosecution history record, an examiner must provide clear explanations of all actions taken by the examiner during prosecution of an application." MPEP 707.07(f). Clearly, the explanations provided in an Office Action should relate to the application in fact being examined, not a different application. However, in the case of the present application, because portions of at least two rejections containing references inapplicable to the present application appear to have been pasted verbatim from the explanation of rejections made in a completely unrelated application, namely Application 12/001,043, the record is unclear as to the extent to which the 35 U.S.C. 112 first and second paragraphs made in the Office Action of March 9, 2009 and maintained in the Office Action of December 17, 2009 were due to supposed deficiencies in the present application or the supposed deficiencies of Application 12/001,043.

Although the use of form paragraphs, for example, might be appropriate for noting certain deficiencies in an application, Applicants submit that it can never be appropriate to include in reasons for rejecting an application a pasted discussion of the substantive content of an

entirely different application. Even when a rejection is prepared by pasting into the Office Action a form rejection and filling in the blanks, this is a questionable practice. As a result, it unclear whether the Examiner has given any consideration to the content of the application that is actually being examined. Yet, according to the record as it presently stands, when considering the *Wands* factor of the "amount of direction provided by the inventor" in connection with the enablement rejection, a discussion was provided of the guidance provided by the applicant of a different patent application was considered, and in making the indefiniteness rejection, that the definitions of terms used in a different patent application were considered. Since it is clear that the remainder of the enablement rejection was prepared from the rejection made in Application 12/001,043 by substituting a few words applicable to the present application, it is unclear to what degree, if any, the disclosure of the present application was, in fact, taken into account when making the rejection.

The Office Action dated December 17, 2009 failed to remedy the deficiencies of the March 6, 2009 Office Action, as only a cursory response was provided to Applicants' detailed traversal of the reasons the rejections. MPEP 707.07(e) instructs that "[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it." However, the Office Action failed to address many of the arguments presented by Applicants with respect to the enablement rejection, and failed to discuss the actual definitions in the specification with respect to the indefiniteness rejection. For example, the Office Action did not address Applicants' concern regarding the out-of-context discussion of "triazalopyrimidines and pyrazolopyrimidines" and that the claims were rejected because to the supposed indefiniteness of terms they did not contain. These errors were dismissed as "typographical errors" without further explanation.

Applicants submit that neither of the Office Actions of March 6, 2009 or December 17, 2009 was prepared in accordance with the Office's proper standards, and that either or both Office Actions should properly be vacated in order to establish a record where it is clear that the reasons for patentability (or any reasons for rejection) are based on the disclosure of the present application and not (for example) the unrelated application having Ser. No. 12/001,043. The Office Action dated December 17, 2009 should be vacated for the additional reason that the

Office Action, clearly did not fully take note of and respond to Applicants' arguments as required by MPEP 707.07(f) when maintaining the enablement and indefiniteness rejections.

IV Conclusion

In view of the foregoing, Applicants ask that the Director to require that the finality of the Office Action dated December 17, 2009 be withdrawn. Applicants also ask that the propriety of the Office Actions dated March 9, 2009 and December 17, 2009 be considered as discussed above, and that either or both of the Office Actions vacated.

Please apply any charges or credits to Deposit Account No. 06-1050 referencing Attorney's Docket No. 20750-0007US1 / 034.US5.PCT.

Respectfully submitted,

Date: February 17, 2010

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Appendix A

Office Action Dated March 6, 2009 in Application 12/001,043 (beginning p. 6 line 1).	**Office Action Dated March 9, 2009 in the Present Application (beginning p. 7 line 9)**
1) *Amount of guidance provided by Applicant.* The Applicant has demonstrated within the application how to make triazolopyrimidines and pyrazolopyrimidines. However, there is no working example of any compounds with R groups other than previously mentioned nor has applicant demonstrated any N-oxides, prodrugs, polymorphs or formulations. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However...there is no evidence that such compounds exist...the examples of the '881 patent do not produce the postulated compounds...there is...no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.	1) *Amount of guidance provided by Applicant.* The Applicant has demonstrated within the application how to make triazolopyrimidines and pyrazolopyrimidines. However, there is no working example of any compounds with R groups other than previously mentioned nor has applicant demonstrated any N-oxides, prodrugs, polymorphs or formulations. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However...there is no evidence that such compounds exist...the examples of the '881 patent do not produce the postulated compounds...there is...no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly. * The present application, in fact, does **not** discuss "triazolypyrimidines" or "pyrazolopyrimidines" or how to make such compounds.

Office Action Dated March 6, 2009 in Application 12/001,043 (beginning p. 12 line 12).	**Office Action Dated March 9, 2009 in the Present Application (beginning p. 7 line 9)**
The scope of "heteroaryl" and "heterocycloalkyl" requires clarification. Applicants' examples in the specification are not limiting. Applicants have not defined these terms with reasonable clarity. See definitions on p.10-14 of the specification. Where applicants define terms with a special meaning, they must set out the special definition with "reasonable clarity, deliberateness and precision". Note *Teleflex v. Ficosa*, 63 USPQ2d 1374; *Rexnord Corp v. Laitram Corp.* 60 USPQ2d 1851 and MPEP 2111.01. The terms are defined with non-limiting examples making them impossible to pin down. For example, when one states C_1-C_4 alkyl, there are a small finite number of possibilities that exist in that set. One ordinarily skilled in the art realizes and understands this. However when one states, "heterocycles" optionally substituted and then provides a list of well over 50 examples and states the list is non-limiting, how can this be considered definite? One skilled in the art could instantly envision well over one hundred 100 ring systems that qualify under this broad, vague definition. Does the applicant wish to claim a thiophene or a triazolopyrimidine? Applicant must narrow such broad terminology by either eliminating such a broad definition or by inserting the specific ring systems they wish to cover into the claim themselves. These arguments also apply to definitions within the specification which contain these terms, such as "heterobicycloalkyl," "heterobicycloalkylalkyl" or "heterocycloalkylalkyl."	The scope of "heteroaryl" and "heterocycloalkyl" requires clarification. Applicants' examples in the specification are not limiting. Applicants have not defined these terms with reasonable clarity. See definitions on p.16 of the specification. Where applicants define terms with a special meaning, they must set out the special definition with "reasonable clarity, deliberateness and precision". Note *Teleflex v. Ficosa*, 63 USPQ2d 1374; *Rexnord Corp v. Laitram Corp.* 60 USPQ2d 1851 and MPEP 2111.01. The terms are defined with non-limiting examples making them impossible to pin down. For example, when one states C_1-C_4 alkyl, there are a small finite number of possibilities that exist in that set. One ordinarily skilled in the art realizes and understands this. However when one states, "heterocycles" optionally substituted and then provides a list of well over 50 examples and states the list is non-limiting, how can this be considered definite? One skilled in the art could instantly envision well over one hundred 100 ring systems that qualify under this broad, vague definition. Does the applicant wish to claim a thiophene or a triazolopyrimidine? Applicant must narrow such broad terminology by either eliminating such a broad definition or by inserting the specific ring systems they wish to cover into the claim themselves. These arguments also apply to definitions within the specification which contain these terms, such as "heterobicycloalkyl," "heterobicycloalkylalkyl" or "heterocycloalkylalkyl." * The claims and specification of the present application do **not** include or define any of the terms: "heterocycloalkyl", "heterobicycloalkyl", "heterobicycloalkylalkyl" and "heterocycloalkylalkyl.".

Appendix B

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/001,043	12/07/2007	Christoph Steeneck	A-1318-US-DIV	1816

30174 7590 03/06/2009

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EXAMINER	
MURRAY, JEFFREY H.	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
03/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/001,043	STEENECK ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/7/2007; 2/1/2008; 3/11/2008; 10/27/2008; & 11/11/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation Sheet (PTOL-326) Application No.

DETAILED ACTION

1. This action is in response to an election from a restriction requirement filed on November 26, 2008. There are fourteen claims pending and fourteen claims under consideration. Claims 2, 3 and 17 have been cancelled. This is the first action on the merits. The present invention relates generally to amide containing heterobicyclic metalloprotease inhibiting compounds, and more particularly to heterobicyclic MMP-13 inhibiting compounds. Election was made **without** traverse in the reply filed on November 26, 2008. Therefore this restriction is considered proper and thus made **FINAL**.

Priority

2. Acknowledgment is made of applicant's claim for domestic priority. The current application, 12/001,043, filed on December 7, 2007, is a division of application 11/602,140, filed on November 20, 2006, which is a continuation-in-part of application 11/440,087, filed on May 22, 2006, which claims domestic priority to U.S. Provisional Applications 60/734,991, filed on November 9, 2005; 60/706,465, filed on August 8, 2005; and, 60/683,470, filed on May 20, 2005.

Specification

3. Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class.

For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. Complete revision of the content of the abstract is required on a separate sheet.

4. The specification (including the abstract and claims), and any amendments for applications, except as provided for in 37 CFR 1.821 through 1.825, must have text written plainly and legibly either by a typewriter or machine printer in a nonscript type font (e.g., Arial, Times Roman, or Courier, preferably a font size of 12) lettering style having capital letters which should be at least 0.3175 cm. (0.125 inch) high, but may be no smaller than 0.21 cm. (0.08 inch) high (e.g., a font size of 6) in portrait orientation and presented in a form having sufficient clarity and contrast between the paper and the writing thereon to permit the direct reproduction of readily legible copies in any number by use of photographic, electrostatic, photo-offset, and microfilming processes and electronic capture by use of digital imaging and optical character recognition; and only a single column of text. See 37 CFR 1.52(a) and (b).

The application papers are objected to because pages 104, 106 and 119 of the specification contain illegible structures. Examiner has attempted to magnify and enhance the page for clarification but to no avail. A legible substitute specification in compliance with 37 CFR 1.52(a) and (b) and 1.125 is required.

5. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Objections

6. Claims 6, 7, 11 and 12 are objected to because of the following informalities:

The claims do not separate the elements of their Markush groups with either a comma or semi-colon. Appropriate correction is required.

7. Claim 13 is objected to because of the following informalities:

The claim does not end with a period. Under MPEP 608.01(m), "Each claim begins with a capital letter and ends with a period." Appropriate correction is required.

8. Claim 15 is an independent claim that claims a species of the generic claim. Multiple inventions may not be claimed in a single application unless they are species claims which are dependent upon the larger, generic claim, see C.F.R. § 1.141(a). Examiner recommends applicant make this claim dependent from Claim 1, or a broader genus claim from which they may depend. No new matter is permitted. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 4-14 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a bicyclic amide where R^2 and R^{20} are hydrogen; R^4 is hydrogen, halogen, OH, SH, $C(O)NH_2$, or NH_2; and R^1 and R_{21} are optionally substituted arylalkyl, cycloalkylalkyl, bicycloarylalkyl, or heterobicycloarylalkyl, does not reasonably provide enablement for all of the other R groups listed nor any N-oxides, prodrugs, polymorphs or formulations within the broad Claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (United States v. Teletronics Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See Ex parte Forman 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* The Applicant has demonstrated within the application how to make triazolopyrimidines and pyrazolopyrimidines. However, there is no working example of any compounds with R groups other than previously mentioned nor has applicant demonstrated any N-oxides, prodrugs, polymorphs or formulations. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However...there is no evidence that such compounds exist...the examples of the '881 patent do not produce the postulated compounds...there is...no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

The quantity of experimentation needed to make or use the invention must be considered to determine if undue experimentation is present. With regard to quantity of experimentation needed, (note Wolff et. al., "Burger's Medicinal Chemistry and Drug Discovery," 5th Ed. Part 1, pp. 975-977 (1995) provided with this action), which emphasizes the many experimental factors for consideration for a successful prodrug as well as the difficulty in extrapolating data from one species to another. "Extensive development must be undertaken to find the correct chemical modification for a specific drug. Additionally, once a prodrug is formed, it is a new drug entity and therefore requires extensive and costly studies to determine safety and efficacy." Banker, et. al.,

Modern Pharmaceuticals, p.596. In view of all these factors undue experimentation would be required to practice the invention.

2) *Unpredictability in the art.* It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

Morphological forms of the compound, or "polymorphs," are the ability of a substance to exist in two/more crystalline phases that have different arrangement and/or conformation of molecules in a crystal lattice.

Screening of pharmaceuticals early on in drug discovery to find out all possible solid forms has significant connotations. (Chawla et. al. Current Research & Information on Pharmaceutical Science, 2004, 5(1), p. 9, col.2, para.1) When designing formulations, it is imperative to know which crystal form of a drug is present at the various stages of a process. "It may be possible that if one polymorph of an active pharmaceutical ingredient, or API, is responsible for activity, another form may be less active, inactive, toxic, or have some other properties of interest." (Chawla et. al.; p. 9, col.2, para.3)

Polymorphs can exhibit many types of differences in their physical properties such as a) packaging; b) thermodynamic; c) spectroscopic; d) kinetic; e) surface; and, f) mechanical properties. (Chawla et. al.; See Table 1, p. 10) These properties offer scientists the opportunity to manipulate bioavailability. It is important to determine if there are phase transformations occurring during processing as well as what crystal form is present in the final drug product. (Newman et. al.; Drug Discovery Today; 2003, 8(19) p. 898, col.2, Para.3.)

While the Applicant has demonstrated within the application how to make the compounds of Formula I, the applicant has not shown any useful data or guidance that would define a particular polymorph that would be biologically active. The applicant has inferred within the specification that any "morphological forms of the compound" would be acceptable. This can clearly not be the case. A contrasting example to this would be chloramphenicol palmitate (CAP). CAP exists in a form A and B. The metastable "form B" of CAP has an eight-fold higher bioactivity than "form A." Yet if "form B" is

administered to humans, it can cause potentially fatal side effects. (Chawla et. al.; p. 9-10). Also a variety of dosage forms are available for pharmaceutical products. (Newman et. al.; p. 899, col.2, Box 1) A polymorph can affect the key solid-state parameters. For example, the drug substance in a tablet formulation will be significantly different than those for an oral suspension or inhalation product. (Newman et. al.; p. 898, col.2, Para.1)

Many functional groups (eg. hydroxy, amino groups) present in drugs are capable at least in theory to being derivatized but determining what is a prodrug (and what is not) requires knowledge of an intended effect (i.e. modification of an undesirable property in the parent drug- poor solubility, poor bioavailability, poor shelf-life) which is never identified by the specification.

The scope of N-oxides or prodrugs is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. The choice of an N-oxide or a prodrug will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which ester will be suitable for the instant invention. The application does not provide any guidance for one skilled in the art on how the N-oxide or prodrug converted to active compounds, by what mechanisms and at what site the N-oxide or prodrug will be activated, what *in vivo* enzymes are likely involved in cleaving the protected group, etc.

Applicants provide no reasonable assurance that any and all known prodrugs will have the ability to regenerate in *vivo* to the instant compounds by one or more biological processes. It is not the norm that one can predict with any degree of accuracy a

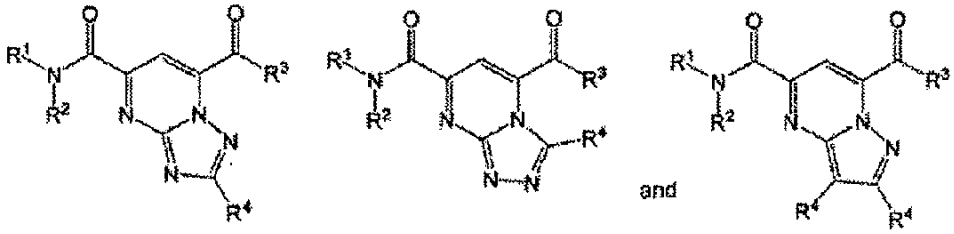
particular ester form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing *in vivo*.

"Formulations" literally would include thousands of additional compounds covered by the claims' scope that has the same molecular formula. In the absence of any guidance in the specification, nothing short of extensive synthesis and testing would be needed to determine if any such "formulations" would have the activity needed to practice the invention.

3) *Number of working examples*. The compound core depicted with specific substituents represents a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any compounds, compositions or pharmaceutically acceptable salts where the R variables were not those mentioned above in the present application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Scope of the claims.* The scope of the claims involves all of the millions of compounds of the following formulas:



thus, the scope of claims is very broad.

5) *Nature of the invention.* The nature of this invention relates generally to to amide containing heterobicyclic metalloprotease inhibiting compounds, and more particularly to heterobicyclic MMP-13 inhibiting compounds.

6) *Level of skill in the art.* The artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions or treating the diseases mentioned.

Claim Rejections - 35 USC § 112, 2nd paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1, 4-14 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The scope of "heteroaryl" and "heterocycloalkyl" requires clarification. Applicants' examples in the specification are not limiting. Applicants have not defined these terms with reasonable clarity. See definitions on p.10-14 of the specification. Where applicants define terms with a special meaning, they must set out the special definition with "reasonable clarity, deliberateness and precision". Note *Teleflex v. Ficosa*, 63 USPQ2d 1374; *Rexnord Corp v. Laitram Corp.* 60 USPQ2d 1851 and MPEP 2111.01.

The terms are defined with non-limiting examples making them impossible to pin down. For example, when one states C_1-C_4 alkyl, there are a small finite number of possibilities that exist in that set. One ordinarily skilled in the art realizes and understands this. However when one states, "heterocycles" optionally substituted and then provides a list of well over 50 examples and states the list is non-limiting, how can this be considered definite? One skilled in the art could instantly envision well over one hundred 100 ring systems that qualify under this broad, vague definition. Does the applicant wish to claim a thiophene or a triazolopyrimidine? Applicant must narrow such broad terminology by either eliminating such a broad definition or by inserting the specific ring systems they wish to cover into the claim themselves. These arguments also apply to definitions within the specification which contain these terms, such as "heterobicycloalkyl," "heterobicycloalkylalkyl" or "heterocycloalkylalkyl."

In addition, "optionally substituted" also falls under this same argument. In the absence of the specific moieties intended to effect modification by "substitution" or attachment to the chemical core claimed, the term "optionally substituted" renders the claim in which it appears indefinite in all occurrences where the applicant fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicant regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed. "Substituted" is a vague and indefinite term because there is no set of possibilities clearly defined in the claims and supported by the specification. This argument is applied to all examples such as "optionally substituted heteroaryl," whereby one skilled in the art would have no idea whatsoever what type of compound applicant was trying to claim with such ambiguous claim language. No new matter permitted. Appropriate correction is required.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1 and 4-16 are provisionally rejected on the ground of nonstatutory anticipatory-type double patenting as being unpatentable over claim 1 of U.S. Patent Application No. 12/001,041. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 1 of U.S. Patent Application No. 12/001,041 embraces the instant claims 1 and 4-16.

15. Claims 1 and 4-16 are provisionally rejected on the ground of nonstatutory anticipatory-type double patenting as being unpatentable over claim 1 of U.S. Patent Application No. 11/602,116. Although the conflicting claims are not identical, they are

not patentably distinct from each other because Claim 1 of U.S. Patent Application No. 11/602,116 embraces the instant claims 1 and 4-16.

The instant claim differs from the copending claim by a more limited genus than the claim of the copending application. However, it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus of the copending application, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus of the copending application since such compounds would have been suggested by the claims of the copending application. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

These are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Conclusion

16. Claims 1 and 4-16 are rejected.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on Mon.-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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